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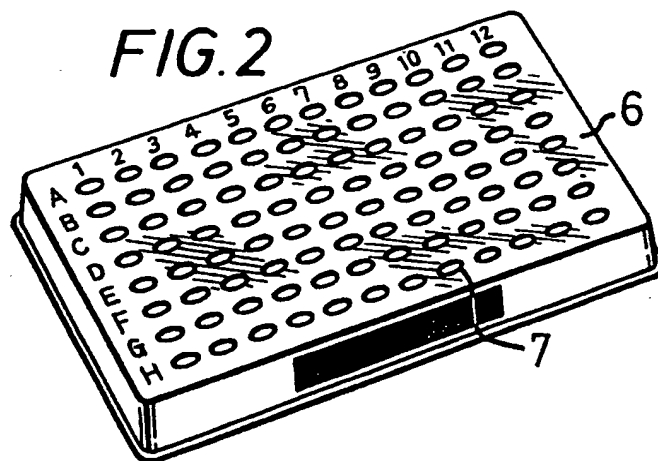
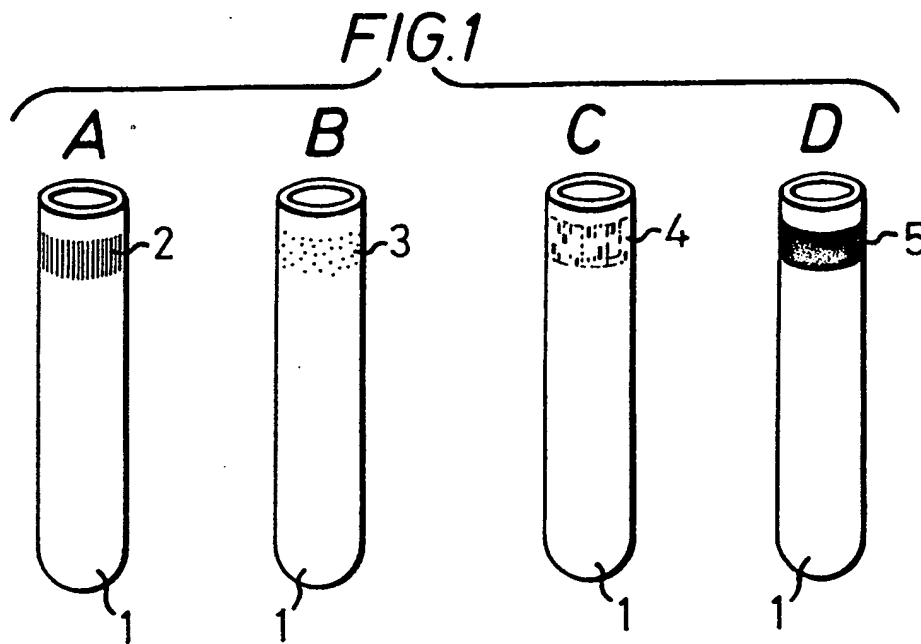
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(54) Immunoassay vessel conveying  
analysis information

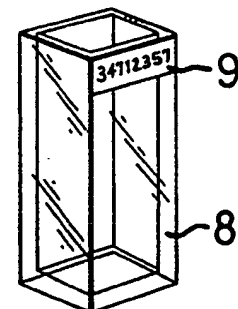
(57) A vessel for use in an immunoassay and containing an insolubilised antibody and a labelled antibody carries also information required for the immunoassay, such as sample information and details concerning the equation defining the calibration curve, whereby the immunoassay can be quickly and accurately performed. The vessel may be a tube, a microtiter plate or cuvette. The insolubilized antibody may be bonded to the inner wall of the vessel or to plastics or glass beads or cellulose fibers.

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**FIG. 3**



## SPECIFICATION

## A vessel for use in immunoassay

- 5 The instant invention relates to a vessel for use in immunoassay of physiologically active substances. 5
- 2. Prior Art*
- The reagents for immunoassay utilizing the antigen-antibody reaction have been employed for determining the quantity of a trace amount of a substance present in body fluids, or for determining the concentration of an administered medicine in blood or urine in an organism. 10
- There are known reagents for practical use in immunoassays which are based on different principles of determination. The reagents for radio-immunoassay (RIA), enzyme-immunoassay (EIA) and fluorescent-immunoassay (FIA) have been widely used because these methods have high sensitivity and high effectiveness in qualitative determination.
- 15 With respect to the reagents used in conventional immunoassays, however, a calibration curve of a substance to be examined must be determined through measurement of the substance at different known concentrations with the reagent prior to each quantitative determination of the unknown concentration of the substance in a specimen. The concentration of the substance of unknown concentration is then determined with reference to the calibration curve thus obtained. 15
- 20 Such a method of measurement is unsuitable in the case of small scale of examination faculties or contingent measurement. Even when a small number of specimens is to be examined, it is necessary to determine a calibration curve through measurement of standard specimens containing the substance at different concentrations as in the case with measurement of a large number of specimens. Therefore, there are drawbacks that the time required for the measurement of one specimen (the time per one specimen being a time obtained through dividing the total measurement time by the number of all the specimens measured) becomes longer and, at the same time, a valuable reagent purified to a high degree is not fully utilized because the standard curve is not repeatedly used in the case of a small number of specimens. 20
- 25 Furthermore, measuring errors and manual mistakes in measurement of the standard specimens may give an inaccurate calibration curve with the result that such an inaccurate standard curve greatly influences the measured values obtained for the specimens of unknown concentrations. Thus, each calibration curve prepared for each measurement of the specimen of unknown concentration to be examined is required to be as accurate as possible for the purpose of improving the reliability of the reagent. 25
- Moreover, instead of a diagnosis based on a single item measurement in clinical examination, it has come to be more important to measure a variety of items and make an overall diagnosis by the combination of the measured results. Consequently, the number of items to be measured is increasing, and therefore clinical examination becomes more and more complicated. Accordingly, it has become more important carefully to check the items to be examined so that the measured value and a calibration curve of each item to be examined may not be mistaken for another. 30
- 35
- 40 Summary of the invention* 40
- An object of the instant invention is, therefore, to provide a vessel for use in an immunoassay, which vessel allows the elimination of the drawbacks encountered by the conventional immunoassay.
- More specifically, the object of the instant invention is to provide a vessel for use in an immunoassay, which vessel allows the determination of the concentration of a specimen with no need to determine the calibration curve every time the measurement is to be done. This avoids time loss and errors in the calibration curve determination, thereby rendering the measurement swift, easy and reliable. 45
- Another object of the instant invention is to provide a vessel for use in an immunoassay, which vessel holds therein a measuring reagent such as an insolubilized antibody, a labelled antibody etc., and the information as to a standard specimen, and a calibration curve of the standard specimen, for instance the type of standard substance, a lot number, a calibration curve and the like which are required for the immunoassay. 50
- Still another object of the instant invention is to provide a vessel for use in an immunoassay, which vessel holds the information of a plurality of items to be examined, whereby manual mistakes such as misrecognition of the items can be avoided.
- 55 A further object of the instant invention is to provide a vessel for use in an immunoassay, which vessel serves as a container adapted to store a measuring reagent, a medium for recording the information necessary for the immunoassay, a place where the reaction takes place, and a vessel for measurement. 55
- Still another object of the instant invention is to provide a vessel for use in an immunoassay, which vessel allows the immunoassay to be automated.
- 60 According to the instant invention, the vessel for use in an immunoassay contains therein a reagent for immunoassay, such as an insolubilized antibody, a labelled antibody, etc.. The reagent may be contained in a freeze-dried condition. The vessel also carries thereon the information as to the standard specimen and the calibration curve thereof, such as the type of standard specimen, the lot number, the calibration curve determined through measurement of the standard specimen at different known concentrations, and the 60

formula corresponding to the calibration curve. The information is carried on the vessel in such a state that it is recorded in an appropriate medium by suitable means, such as magnetic, optical, or the like means.

#### *Brief description of the attached drawings*

- 5 These and other objects and features of the present invention will be well appreciated by a reading of the following description of the invention in conjunction with the attached drawings in which; 5
- Figure 1* is a perspective view of tube-like vessels according to the present invention;
- Figure 2* is a perspective view of a microtiter plate-like vessel according to the present invention; and
- Figure 3* is a perspective view of an optical cell-like vessel according to the present invention. 10

#### *Detailed description of the invention*

- The vessel according to the present invention holds a reagent such as an insolubilized antibody, a labelled antibody, and the like as well as the information useful for the immunoassay, while the vessel serves as a reaction container where the reagent reacts with a specimen to be examined. Further, it may serve as a measuring vessel in case the measurement of the concentration of the specimen is carried out through means such as absorbance of the specimen. In such a case, the information is so carried on the vessel that it may not interfere with the measurement. The vessel may be made of plastic, glass or the like and may be formed in the shape of a cylindrical tube, cuvette, microtiter plate, or the like. The shape and material of the vessel may be selected depending upon the measuring method of the specimen, etc.. 15
- 20 The reagent carried on the vessel comprises an insolubilized antibody which is prepared by bonding an antibody onto a water-insoluble carrier such as plastic or glass beads, cellulose fibres or the like. The reagent may also be carried on the vessel *per se* as a reaction container. 20
- The labelled antibody is prepared by bonding an antibody to a labelling agent which is optically, chemically and/or physically detectable. Generally, enzymes, radioactive isotopes, fluorescent substances and the like may be employed as the labelling agent. The enzyme may be horseradish peroxidase, alkaliphosphatase, -D galactosidase, glucoseoxidase, etc.. The radioactive isotope may be  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^3\text{H}$ , etc.. The fluorescent substance may be fluorescent isocyanate, rhodamine, etc.. 25
- The memory medium for recording the information as to the standard specimen and the calibration curve thereof may include a magnetic recording medium, such as magnetic tape or the like, an optically reading medium such as an optical mark, optical letter, bar code, spot code or the like, or a laser recording medium. 30
- The magnetic recording medium may be prepared by molding a plastic material admixed with a ferromagnetic material, or by forming a thin layer of ferromagnetic material on a plastic film. Before or after the information necessary for the immunoassay is recorded in the magnetic recording medium, it is attached to an appropriate portion of the vessel. A magnetic head is used for recording the information on the magnetic recording medium. The recording medium is magnetized by the magnetic flux which flows from the tip of the magnetic head when current flows through a coil wound around the magnetic head, so that the information is recorded in the magnetic recording medium. 35
- The information may be recorded as a combination of "O" and "I" which may be distinguishably recorded in the different magnetized states.
- 40 When a reading magnetic head approached the recording medium portion magnetized in accordance with the information, the magnetic flux density at the magnetic head changes to induce voltage in the coils. The output voltage is detected through amplification and rectification so as to read the information recorded in the magnetic recording medium. 40
- Any conventional magnetic recording system may be used. Typical examples may include RZ (return to zero) systems in which the magnetized portion and non-magnetized portions are made to correspond to "O" and "I"; NRZ systems (no return to zero) in which "O" and "I" are made to correspond to the different magnetized directions; NRZI (no return to zero inversion) systems in which the "O" and "I" are made to correspond to normal and inverted magnetic flux; PhM (phase modification) systems in which the "O" and "I" are made to correspond to different phases; FM (frequency modification) systems in which the units "O" and "I" are made to correspond to different frequencies, etc.. 50
- The information "O" and "I" may be used as they are, or in coded notation. The coding system may be ISO/CCITT (International Standard Organization/Counsel Committee of International Telegraph and Telephone) code, BCD (Binary coded decimal) code, an EBCDIC (extended binary coded decimal interchange) code, etc.. 55
- The magnetic recording medium may alternatively be a magnetic ink which contains a ferromagnetic material therein. The information is placed directly or indirectly onto the vessel through printing with the magnetic ink. The information thus recorded is read by means of a magnetic ink character reader (MICR). The character printed with the magnetic ink may be in a type of E 13B, CMC 7, or the like. 55
- The optical mark may be a mark formed in a colour (usually black) of low reflection factor on an information medium. The information recorded onto the vessel in the form of optical marks is read by means of a reading head of an optical mark reader. A light beam is irradiated onto the information medium through a glass fibre tube from the reading head and the transmitted light beam or the reflected light beam is received by a photocell through a reading glass fibre tube, so that the mark may be read. 60
- The bar code is a means for representing information on the basis of the number and width of printed bars. 65
- The information is read by the detection of reflected or transmitted light beams as irradiated. A variety of bar 65

codes known as COD 39, UPCA, EAN 13, JAN, etc., can be employed. A code having any other shape, such as a spot, can also be used instead of a bar.

The optical character is a character to be read by an optical character reader, for example, Font A or B of ISO (International Standard Organisation) in which a light beam is applied to the characters, and reflected light is detected by a number of photocells to quantify the characters, whereby the information is read. 5

An optical mark having a circular or oval shape or the like may particularly be called a "spot code". The spot code may, for example, comprise a plurality of vertical lines each having eight locations to be spotted of which seven correspond to the seven unit codes of JIS (Japan Industrial Standard), representing one character, while the eighth location to be spotted is provided for parity check purposes.

10 The presence or absence of a spot is detected by the reflection or transmission of a light beam. The spot which is to be detected by reflected light is formed in a colour of low reflection factor (usually black). In such a case, a light beam is irradiated on the location to be spotted from a light source such as a lamp through, for example, a glass fibre tube, and reflected light is received by a photocell through, for instance, a glass fibre tube, etc.. 10

15 If there is no spot in the irradiated location, a large quantity of reflected beams is detected by the photocell. This is made to correspond to information "O". If, on the other hand, there is a spot in the irradiated location, the quantity of reflected beams is largely reduced, and difficult to be detected by the photocell. This state is made to correspond to information "I". 15

When there is provided a spot code consisting of seven unit codes of JIS and a parity check spot, eight spots can simultaneously be detected to obtain information corresponding to one character, if eight detecting glass fibre tubes and eight photocells are used. Thus, information for each character is successively read from the spot codes to obtain the original character series. 20

When the spot code is read by a transmitted light beam, the spots are formed on a transparent medium with a pigment which allows no transmission of the light beam. A light beam is radiated on the spot code from a light source, and the transmitted light beam is led to a photocell for detection. If there is no spot, a transmitted light beam is detected. This state is made to correspond to information "O". If there is a spot, no transmitted light is detected. This state is made to correspond to information "I". 25

When there is provided a spot code consisting of spots corresponding to the seven unit codes of JIS and a parity check spot, the use of eight photocells makes it possible to detect the presence of eight spots simultaneously and thereby obtain information corresponding to one character. Information for each character is successively read from the spot code to obtain the original character series. 30

As a matter of course, other code systems than the seven unit codes of JIS may also be used to define the spot code.

With optical recording, information may be recorded through forming perforations in a thin metal film by a high energy laser beam or the like. A low energy laser beam or the like is used to detect the perforations for obtaining the information. 35

These information media may be incorporated into the vessel during molding of the vessel, or applied to the vessel through printing or adhesion, etc..

What each vessel carries thereon is information for identifying a standard specimen and the factors which are directly indicative of a standard curve. For example, if a standard curve is regressible to a cubic equation, the values of the four coefficients a, b, c and d in the following equation I are to be carried on the vessel as the information: 40

$$y = ax^3 + bx^2 + cx + d \text{ (cubic curve)} \quad \text{(I).} \quad 45$$

It is known that an immunological reaction is often regressible to a logistic curve. In this case, information on the four coefficients a', b', c' and d' in the following equation II is to be carried on the vessel:

$$y = \frac{a' - d'}{1 + (x/c') b'} + d' \text{ (logistic curve)} \quad \text{(II).} \quad 50$$

These coefficients can be obtained by the "method of least squares" based on measurement of a standard specimen at different concentrations using a reagent of the same lot as used for the subsequent measurement.

It is possible to show any point in a coordinate system directly by a pair of codes if the readings on the x and y axes are coded. 55

The information on the above matters is usually carried on a vessel for each reagent. The vessel may be of various shapes and materials, for example, a glass test tube, a plastic test tube, a microtiter plate, an optical cell or the like. Figures 1 to 3 show by way of example vessels for use in immunoassay according to this invention.

Figure 1 shows several test tubes 1 each carrying information on an outer surface thereof adjacent to the upper end. 60

The information is carried by a bar code 2 (A), a spot code 3 (B), an optical mark 4 (C) and a magnetic tape 5 (D).

Figure 2 shows a microtiter plate 6 carrying information 7 on one side thereof. The microtiter is provided with a plurality of recesses for holding a reagent for immunoassay therein. 65

Figure 3 shows an optical cell 8 carrying information 9 on one side thereof at the upper end.

The information carried on each of these vessels can be read by a magnetic head, optical reader, or the like.

The vessel for use in immunoassay according to this invention has the following advantage:

- 5 Since a calibration curve is preliminarily prepared under strict control, and the information as to the coefficients or equation defining the curve is carried on each vessel, it is possible: 5
- (1) to eliminate any inconvenience involved in the preparation of a calibration curve, for example, a mistake or error in every measurement or in calibration curve preparation, and to eliminate time required as a result of any error in the calibration curve preparation;
- 10 (2) to prevent any human mistake in the selection of a calibration curve for a particular item of examination, even if numerous items have to be examined for each sample; 10
- (3) to accomplish simultaneously the determination of the absorbance of the reaction solution and the reading of the information on the vessel so that the quantity of a specimen having an unknown concentration may be determined more quickly and accurately in accordance with the calibration curve; etc..
- 15 The invention will now be described more in detail with reference to specific experiments. 15

#### EXPERIMENTS:

##### *Vessel for use in the measurement of -fetoprotein (AFP).*

- 20 (a) A polystyrene test tube was washed with a 0.05 M phosphate buffer saline solution (pH 6.4) (hereinafter referred to as PBS). The test tube was charged with 2 ml of a monoclonal AFP antibody [A] (1 mg/ml), and left at 37°C for 30 minutes. It was washed with PBS to provide an anti-AFP antibody [A] sensitized test tube. On the other hand, a monoclonal antibody [B] having a different clone from that of the antibody [A] was labelled with horseradish peroxidase (HRPO Grade 1 of Boehringer Mannheim) in accordance with the method of Nakane *et al.* (Journal of Histochemistry and Cytochemistry, Vol. 22, page 1084 (1974)). This labelled 25
- 25 antibody was then diluted with PBS to 50 fold volume. 1 ml of the diluted solution was charged into the anti-AFP antibody [A] sensitized test tube. The tube was subjected to lyophilization and sealed tightly to provide a vessel for AFP measurement prior to carrying information on a standard curve. In the same manner, a number of test tubes were prepared. 25

- (b) A vessel prepared at (a) above was charged with 0.9 ml of PBS. AFP was diluted with the serum of a healthy human to 1,000, 100, 10 and 1 ng/ml as respective standard solutions. 0.1 ml of each standard 30
- 30 solution was added to the respective vessels, and the reaction was performed for 30 minutes. Upon termination of the reaction, the vessels were washed with a physiological saline containing 0.005% Tween 20, and charged with 2 ml of an enzyme substrate solution containing 50 mg/dl of 5-aminosalicylic acid and 0.01% of hydrogen peroxide. Thereafter, the reaction was further performed for 30 minutes.
- 35 Then, 50 l of 2% sodium azide were added to terminate the reaction. The absorbance of the reaction solution was measured by a spectrophotometer at a wavelength of 500 nm. A logistic regression curve was obtained from the results of the measurement by the method of least squares. 35

- A bar code was formulated from the coefficients of the logistic curve, and printed on paper labels. The labels were attached to the respective vessels prepared at (a) above to provide vessels for use in AFP 40
- 40 immunoassay according to this invention. 40

##### *(c) Example of use of the vessel for AFP immunoassay.*

- One of the vessels prepared at (a) above was charged with 0.9 ml of PBS, and 0.1 ml of a specimen having an unknown AFP concentration was added thereto. The reaction was performed for 30 minutes. Upon 45
- 45 termination of the reaction, the vessel was washed with a physiological saline containing 0.005% of Tween 20, and charged with 2 ml of an enzyme substrate containing 50 mg/dl of 5-aminosalicylic acid and 0.01% of hydrogen peroxide. Thereafter, the reaction was performed for 30 minutes again.

- Then, 50 l of 2% sodium azide were added to terminate the reaction. The absorbance of the reaction solution was measured by a spectrophotometer at a wavelength of 500 nm. The bar code on the vessel was 50
- 50 read by a bar code reader (HEDS-3000 of Yokogawa Hewlett Packard Co.), and the coefficients  $a'$ ,  $b'$ ,  $c'$  and  $d'$  for the logistic regression equation II representing the calibration curve were read. The coefficients and absorbance of the unknown specimen were incorporated into the logistic equation (II), so that the unknown concentration of the specimen was determined.

The following table shows the measured values for the standard solutions, the values of the coefficients in the regression equation, the measured values for the unknown concentration specimens and their concentrations obtained by incorporating the measured values into the regression equation:

## 5 Standard Solutions:

5

	<i>AFP Conc., ng/ml</i>	<i>Measured Value (OD)</i>	
	0.0	0.036	
	20.0	0.168	
	40.0	0.260	
10	80.0	0.360	10
	160.0	0.541	
	320.0	0.779	
	640.0	0.985	

15

## Coefficients in Regression Equation (II);

15

$$y = \frac{a' - d'}{1 + (x/c') b'} + d' \text{ (logistic curve)} \quad (II).$$

$a' = 1649.467184896$   
 $b' = -.8194106157553$   
 $c' = 408.9882457476$   
 $d' = 39.23497407545$

25

25

## Unknown Samples:

	<i>Measured Value (OD)</i>	<i>Concentration (ng/ml)</i>	
	0.556	163.85	
30	0.630	210.14	30
	0.881	457.08	
	0.295	53.48	

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## CLAIMS

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1. A vessel for immunological analysis, said vessel containing an insolubilized antibody and a labelled antibody and carrying information concerning said analysis.
- 40 2. A vessel for immunological analysis as set forth in claim 1, wherein said information includes data identifying a calibration curve for said analysis.
3. A vessel for immunological analysis as set forth in claim 1, wherein said information includes data identifying a substance to be analyzed.
4. A vessel for immunological analysis as set forth in claim 1, wherein said information is carried by an
- 45 information storing medium from which said information is magnetically readable.
5. A vessel for immunological analysis as set forth in claim 4, wherein said medium is selected from among magnetic tape and magnetic ink.
6. A vessel for immunological analysis as set forth in claim 4, wherein said medium comprises a portion of a wall of said vessel.
- 50 7. A vessel for immunological analysis as set forth in claim 4, wherein said medium is attached to a wall of said vessel.
8. A vessel for immunological analysis as set forth in claim 5, wherein said magnetic ink is applied directly to a wall of said vessel.
9. A vessel for immunological analysis as set forth in claim 1, wherein said information is carried by an
- 55 information storing medium from which said information is readable by an optical reading machine.
10. A vessel for immunological analysis as set forth in claim 9, wherein said information is recorded on said medium in a form selected from the group consisting of a bar code and an optical mark or character.
11. A vessel for immunological analysis as set forth in claim 9, wherein said medium comprises a portion of a wall of said vessel.
- 60 12. A vessel for immunological analysis as set forth in claim 9, wherein said medium is attached to a wall of said vessel.
13. A vessel for immunological analysis as set forth in claim 12, wherein said medium comprises a thin metal film wherein said information is recorded in a form of perforations therein.
14. A vessel for immunological analysis as set forth in claim 1, wherein said vessel comprises an optical
- 65 cell.

65

15. A vessel for immunological analysis as set forth in claim 1, wherein said vessel comprises a microtiter plate.
16. A vessel for immunological analysis as set forth in claim 1, wherein said vessel comprises a test tube.
17. A vessel for immunological analysis as set forth in claim 1, wherein said insolubilized antibody is one  
5 bonded to an inner wall of said container. 5
18. A vessel for immunological analysis as set forth in claim 1, wherein said insolubilized antibody is one bonded to glass or plastic beads.
19. A vessel for immunological analysis as set forth in claim 1, wherein said labelled antibody is one bonded to an enzyme, radioactive isotope or fluorescent substance.
- 10 20. A vessel for immunological analysis as set forth in claim 1, wherein said insolubilized and labelled 10 antibodies are contained in a freeze-dried condition.
21. A method for performing immunological analysis comprising performing said immunological analysis in a vessel, said vessel containing an insolubilized antibody and a labelled antibody and carrying information concerning said analysis thereon.
- 15 22. A method as set forth in claim 21, wherein said vessel comprises an optical cell and the absorbance of 15 said reacted test solution is measured in said vessel.
23. A method as set forth in claim 21, wherein said insolubilized antibody and said labelled antibody are stored in said vessel in freeze-dried form prior to performing said analysis.
24. A method as set forth in claim 21, wherein said information is carried by an information storing  
20 medium from which said information is magnetically readable. 20
25. A method as set forth in claim 24, wherein said medium is selected from among magnetic tape and magnetic ink.
26. A method as set forth in claim 24, wherein said medium comprises a portion of a wall of said vessel.
27. A method as set forth in claim 24, wherein said medium is attached to a wall of said vessel.
- 25 28. A method as set forth in claim 25, wherein said magnetic ink is applied directly to a wall of said 25 vessel.
29. A method as set forth in claim 21, wherein said information is carried by an information storing medium from which said information is readable by an optical reading machine.
30. A method as set forth in claim 29, wherein said information is recorded on said medium in a form  
30 selected from the group consisting of a bar code and an optical mark or character. 30
31. A method as set forth in claim 29, wherein said medium comprises a portion of a wall of said vessel.
32. A method as set forth in claim 29, wherein said medium is attached to wall of said vessel.
33. A method as set forth in claim 29, wherein said medium comprises a thin metal film wherein said information is recorded in a form of perforations therein.
- 35 34. A method as set forth in claim 21, wherein said insolubilized antibody is bonded to an inner wall of 35 said container.
35. A method as set forth in claim 21, wherein said insolubilized antibody is bonded to glass or plastic beads.
36. A method as set forth in claim 21, wherein said labelled antibody is bonded to an enzyme, radioactive  
40 isotope or fluorescent substance. 40
37. A vessel for immunological analysis substantially as herein described and with reference to the accompanying drawings.
38. A method as claimed in claim 21 and substantially as described in any one of the specific experiments hereinbefore set forth.



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